

Naval Health Research Center

HYPOTHERMIA

*R. S. Pozos
P. A. Iaizzo
D. F. Danzl*

Report No. 93-8

20000619 013

Approved for public release: distribution unlimited.

NAVAL HEALTH RESEARCH CENTER
P.O. BOX 85122
SAN DIEGO, CALIFORNIA 92186-5122

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND



DTIC QUALITY INSPECTED 4

Hypothermia

by

R.S. Pozos, Ph.D.
Naval Health Research Center
Thermal Division
San Diego, California

P.A. Iaizzo, Ph.D.
University of Minnesota
School of Medicine
Department of Anesthesiology
Minneapolis, Minnesota

D.F. Danzl, M.D.
University of Louisville
School of Medicine
Emergency Department
Louisville, Kentucky

Report number 93-8, supported by the Naval Medical Research and Development Command, Office of Naval Technology, Department of the Navy. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. Approved for public release, distribution unlimited.

Man has a complex, physiologically coordinated system designed to maintain a core temperature of 37°C. Despite the amazing capacity and responsiveness of the thermoregulatory system, human health is frequently challenged by cold stress leading to hypothermia. Recently, unpredictable climatic conditions were responsible for the deaths of five mountaineers on Mount McKinley. The incidence of hypothermia is not limited to cold latitudes. Hypothermia may occur in even tropical regions. For example, in Tijuana, Mexico, in 1989, an usually cold night resulted in a number of hypothermic deaths. These incidents are only two examples of the countless times environmental conditions have caused hypothermia that resulted in injury or death. Add to this the many cases of cold water exposure and hypothermia secondary to trauma, and it is clear that accidental hypothermia due to environmental cold conditions is a very real concern for clinicians.

External factors, however, are not the only causes of hypothermia. Indeed, hypothermia is frequently the result of anesthesia or drugs that interfere with internal thermoregulatory mechanisms. Annually, between one and seven million patients in postanesthetic care units experience mild hypothermia (Voelsang and Hayes 1989). The expense and threat to human health, especially in patients with compromised conditions associated with cardiovascular, endocrine, and degenerative disorders, is just beginning to be recognized and evaluated (Feroe and Augustine 1991). This review will focus on the current understanding of human thermoregulation, the common basis for understanding various categories of hypothermia, and therapeutic approaches to its management and treatment.

Physiology of Thermoregulation in Cold Environments

The body's physiologic systems are most efficient at 37°C; any drop in core temperature will decrease overall functioning. Core temperature decreases of 1 to 2°C (36° to 35°C) define the initial stage of hypothermia. When core temperature reaches 25°C, ventricular fibrillation or asystole can occur spontaneously (Bangs 1984). Although it is commonly assumed that hypothermia

occurs more frequently in northern latitudes, it is a concern in all settings and seasons. Even at a "comfortable" ambient temperature of 22°C, there is a substantial temperature gradient of 15°C between the core and the environment. Without adaptive behavioral and physiological responses, the core temperature will eventually fall. The "core" is generally considered the "collective" temperature of the internal organs (Nicholson and Iserson 1991). The right atrium, esophagus, rectum, vagina, bladder, and tympanic membrane are some of the sites used to measure core temperature. Although the right atrium is considered the most accurate site, it is not practical in most circumstances. Other sites have disadvantages as well; the rectal site will lag other core temperatures, such as esophageal (Nicholson and Iserson 1991); the esophageal reading may be falsely elevated during heated inhalation (Kaufmann 1982); tympanic measurement, considered by some to indicate brain temperature, is affected by environmental and mechanical factors, such as facial fanning and cerumen (Shiraki et al. 1988).

Models of thermoregulatory systems are used to explain multiple responses to cold stress, hypothermia, and rewarming (Bligh 1985). During cold stress, thermal receptors of the skin and viscera (heart, liver) transmit their respective inputs to specific brain and spinal cord sites. These signals are then integrated with brain and spinal cord temperature (Figure 1). These data are then compared to a preset thermal range (set point) programmed to maintain a certain core (brain, visceral) temperature. Supporting physiological evidence for the set-point process is controversial (Bligh 1985). Although the hypothalamus contains major nuclei that integrate thermal signals, other sites (e.g., spinal cord) also help coordinate cold responses. For example, shivering can be induced in "spinal" animals (Simon 1966), and recently the clonus in paraplegic patients has been shown to be identical to human shivering (Pozos and Iaizzo 1991). In all models of thermoregulation in a cold environment, the cold-sensing skin receptors play a principal role in triggering heat conservation by both behavioral and physiological responses. In addition to activation of the

peripheral cold receptors, visceral and brain temperature receptors also contribute.

Behavioral manifestations such as emotional or motor responses are considered the first reactions to cold stimulus. The mechanism for these behavioral changes is not well understood but are critical for survival and vary tremendously between individuals. Initial cold activation of the thermoregulatory system includes tachycardia, vasoconstriction (resulting in hypertension and thermogenesis), shivering, hyperventilation, and increased catecholamine release (resulting in increased core temperature). Vasoconstriction of the periphery, in effect, increases the periphery's insulating layer, which protects the core and creates additional thermogenesis. In addition, shivering thermogenesis from muscle contraction will maintain core temperature. Simultaneously, release of catecholamines and thyroid hormones increase cellular metabolism (Paton 1983). Paradoxically, protective clothing (gloves, parkas, etc.), whose purpose is to minimize cold receptor activation, may promote the insidious onset of hypothermia. The swimmer in cold water may become hypothermic as the wet suit and his or her swimming will inhibit shivering. Similarly, placing warm blankets on a shivering patient blunts the thermal drive toward increased thermogenesis. In both of these cases, the lack of cold-receptor activation will prevent heat-producing and -retaining responses to counteract the cold environmental challenge.

Various drugs (e.g., ethanol or anesthetics) will influence thermoregulation and cause physiological responses similar to those triggered by a cold challenge. Since "cold-minimizing" responses are triggered by neural integrating centers monitoring a difference between core and periphery, thermal responses may also be triggered by cooling the core relative to the skin. Ingestion of a cold slush, or inspiring cold air (as in the case of deep sea divers), will cause a decrease in core temperature and initiate the same responses as cooling the skin.

Hypothermia may also result from increased body heat associated with exercise in an overdressed situation that results in sweating, dehydration, and subsequent body cooling.

As hypothermia develops, thermoregulatory systems are initially excited, then progressively depressed (Table 1) (Paton 1983). There is significant individual variability in the clinical manifestations, but whether hypothermia is induced clinically or accidentally, this sequence is commonly the final result. For example, some hypothermic subjects at 34°C rectal temperature will be completely coherent, whereas others will exhibit signs of short-term memory deficit; however, both will expire eventually due to asystole or ventricular fibrillation when their core temperature reaches values in the range of 25-28°C.

Classification

Hypothermia can be classified into two main types: accidental and iatrogenic (clinical).

Accidental hypothermia is a consequence of two predominant mechanisms (Golden 1983). One involves the relatively cold environment overwhelming the normal physiological and behavioral responses to cold stress (primary hypothermia) (Figure 2). In the other, some or all of the physiological systems that maintain a core temperature of 37°C are compromised (secondary hypothermia) and thus cannot respond appropriately to the thermal environment (Figure 3). Secondary hypothermia is brought on by one or more of three body processes: decreased heat production, impaired thermoregulation, or increased heat loss (e.g., vasodilation). As Table 2 illustrates, secondary hypothermia is a major challenge to physicians, since it actually masks the underlying pathology. Although many causes induce accidental hypothermia, most cases are drug-induced. For example, ethanol intoxication is a leading cause of hypothermia, since it promotes vasodilation and, more importantly, blunts normal behavioral responses.

Iatrogenic hypothermia is the result (deliberate or inadvertent) of physician action in which the patient is cooled, usually by surgical/anesthetic

manipulation resulting in temperatures as low as 30°C. Some iatrogenic cooling, such as in cardiac bypass surgery, utilizes hypothermia's multifaceted effects on physiologic systems to enhance recovery in situations that would be lethal under normothermic conditions. Due to the sheer number of operations performed each year, iatrogenic hypothermia is by far the largest category.

Since patients may tolerate various levels of body cooling, hypothermia has been divided into three categories - mild, moderate, and severe (Table 1) based on the presence of certain physiological signs at various core temperatures. The rationale for this division is based on the observation that individuals with chronic exposure experience significant fluid and electrolyte changes. Hypothermia may be induced over an acute (< six hours) or a chronic (> six hours) period of time (Golden 1983); this separation is arbitrary.

Although accidental and iatrogenic are the predominant types of hypothermia, other classifications have been used to describe various environmental situations or unique patient conditions that promote hypothermia. Submersion hypothermia, for example, denotes that the victim drowns in cold water, and because of rapid core cooling, has a chance for recovery that may extend to 45 minutes (impossible in a normothermic situation). Water immersion hypothermia, induced by the person floating in water, signifies a much faster cooling rate than that caused by ambient air, and poses different rewarming problems. Mountain hypothermia denotes that the cold-stressed climber may suffer from sleep deprivation, dehydration, malnourishment, and low oxygen concentration. Pediatric hypothermia refers to the following characteristics of this patient group: large surface area to volume, inability to shiver, and underdeveloped central nervous system. Urban or geriatric hypothermia emphasizes the elderly's lack of mobility, decreased muscle mass, dehydration, and possible malnutrition.

Hypothermia's Double-Edged Sword

Although hypothermia may eventually lead to death, depending upon its degree and the rate at which it is induced, it can extend the limits of survivability by: 1) depressing metabolism, and subsequently diminishing oxygen demand and delivery; or 2) altering other systems, such as membrane stability (Leonov et al. 1990). Consequently, treatment of the hypothermic victim poses an interesting clinical challenge. He or she may survive pathophysiologic conditions (e.g., hypoxia) that would be otherwise lethal (i.e., during normothermia). However, during the rewarming process, the increased core temperature may trigger cold-suppressed pathology. Nevertheless, cases of patient survival (with core temperatures as low as 15.2°C in primary, and 9°C in iatrogenic hypothermia) are striking examples of the degree to which body cooling can be reversed (Danzl, Pozos, and Hamlet 1989).

Pre-Hospital Management

Pre-hospital hypothermic resuscitation is as important as in-hospital management. The abiding principles are governed by recognition of the depressive effects of low body temperature on cardiopulmonary physiology and metabolism. These factors dictate the mechanics of rescue, examination, insulation, and transport (Steinman 1986). Core temperature measurement (e.g., rectal, esophageal) in the field is currently impractical, pending evaluation and refinement of new techniques. If circumstances suggest significant or chronic exposure, an irritable myocardium and metabolic depression are likely. In chronic hypothermia, transporting the patient is extremely risky (Solomon et al. 1989).

Accurate assessment of ventilation and perfusion is critical in the field. Pre-hospital triage should be reserved for patients for whom the potential benefit of immediate cardiac pulmonary resuscitation (CPR) clearly exceeds the attendant hazards of transport and delay. Profound depression of respiration mimics apnea. Similarly, extreme bradydysrhythmias, coupled with peripheral

Initiate CPR in accidental hypothermia unless:

1. "Do Not Resuscitate" status is documented and verified.
2. Obvious lethal injuries are present.
3. Chest wall depression is impossible.
4. Any signs of life are present.
5. Rescuers are endangered by evacuation delays or altered triage conditions.

Optimal field rewarming is an art based on practicality, and its primary aim is temperature stabilization. It can increase the risk of initiating elevated resultant electrolytes (hyperkalemia), cardiovascular (ventricular fibrillation) responses, or a hypothermia-suppressed pathology that might not be treatable in the field. Hypothermia induces changes in the electrocardiogram which might not be correlated with cardiac muscle function and consequent perfusion. This phenomena is called perfusing rhythms. In patients with perfusing rhythms, field thermal stabilization and passive external rewarming (PER) will minimize further heat loss via radiative, conductive, convective, and evaporative routes (Mills 1980). When available, heated, humidified oxygen inhalation will eliminate respiratory heat loss, but will also suppress shivering. Most patients will benefit from both supplemental oxygenation, and a crystalloid challenge with heated 5% dextrose in normal saline (Shields and Sixsmith 1990). If prolonged field exposure is inevitable, external truncal heat application may be the only viable option (Hamlet 1987).

Hospital Management

Hypothermia diagnosis should be confirmed by core temperature measurement and continuous monitoring of all vital signs (Nicholson and Iserson 1991). Pre-rewarming considerations should focus on clinical presentations that are inconsistent with hypothermia (Table 2). Disproportionate tachycardia implies hypovolemia, hypoglycemia, or a drug overdose. Inappropriate hyperventilation may reflect a central nervous system lesion or organic acidosis (DKA, LA). A loss of consciousness inconsistent with the temperature may result from

Hospital Management

Hypothermia diagnosis should be confirmed by core temperature measurement and continuous monitoring of all vital signs (Nicholson and Iserson 1991). Pre-rewarming considerations should focus on clinical presentations that are inconsistent with hypothermia (Table 2). Disproportionate tachycardia implies hypovolemia, hypoglycemia, or a drug overdose. Inappropriate hyperventilation may reflect a central nervous system lesion or organic acidosis (DKA, LA). A loss of consciousness inconsistent with the temperature may result from toxicologic, traumatic, or infectious impairment of the central nervous system. Conversely, areflexia ascribed to hypothermia may, in fact, indicate spinal cord injury (Danzl, Pozos, and Hamlet 1989).

In patients without protective airway reflexes, pre-oxygenation and gentle handling during tracheal intubation may help avert arrhythmias (Figure 4). In a multicenter survey of 428 cases, 97 of 117 intubated patients were below 32°C (considered the key temperature to induce ventricular fibrillation), and yet, none developed ventricular fibrillation (Danzl et al. 1987). Since hypothermia influences smooth muscle activity, a cold-induced ileus and rectal spasm invalidate abdominal examination. Gastric and bladder catheterization help assess and address expected ileus and fluid shifts.

Continuing hematologic and electrolyte evaluation is necessary, except in mild cases. There appear to be no safe clinical predictors of trends or values. Ultrastructural cellular damage, coupled with altered perfusion, often explains a variety of elevated serum enzymes, amylase, and lipase (Danzl et al. 1987).

Predicting the acid-base profile of hypothermic patients is difficult. The pH is usually acidotic due to: 1) respiratory system depression, 2) increased solubility of CO₂ in blood as temperature decreases, 3) lactate generation from shivering and decreased tissue perfusion, and 4) acid excretion. However, in one study of 135 cases, 32% were acidotic, and 25% alkalotic (Miller, Danzl, and Thomas 1981). The controversy of whether to correct arterial blood gas parameters for decreasing core temperature has been resolved. Relative acid-base

balance is reflected by an uncorrected pH=7.4, and pCO₂=40 mm Hg at all temperatures (Swain 1988; White 1983). This is termed the "alpha-stat" or "ectotherm" approach (Kroncke, Nichols, and Mendenhall 1986). Since the neutral point of water at 37°C is pH=6.8, a 0.6 pH unit offset normally exists between the cell and body fluids. Maintaining this offset under progressively declining temperatures results in the relative alkalinity of tissues, since the neutral point of water rises as the temperature drops. This process optimizes enzymatic functions and preserves distribution of critical metabolic intermediates (pK 4.6 + 9.2), while maintaining transport systems and cellular waste disposal (Delaney et al. 1989). Conversely, maintaining the temperature-corrected pH at 7.4 and 40 mm Hg during hypothermia depresses cerebral blood flow, coronary blood flow, and cardiac output, and increases the incidence of ventricular fibrillation. Thus, temperature correction of arterial blood gases is unnecessary and potentially deleterious.

Although it is often thought that hypothermia-induced vasoconstriction reduces bleeding, hypothermia actually enhances the tendency to bleed. Cold hemagglutination and coagulopathies reflect a variety of processes not well-understood (Poulos and Mollitt 1991; Ferrara et al. 1990). Platelet activity declines in a linear fashion and fibrinolysis increases as temperature decreases. A "DIC-type" syndrome is characterized by a prolonged prothrombin time, partial thromboplastin time, and bleeding time with hypofibrinogenemia (Patt, McCroskey, and Moore 1988). Hypothermia also retards the coagulation enzymatic cascade, stiffens red blood cells, and induces primary fibrinolysis (Reed et al. 1990). Clinically significant thrombocytopenia may result from both direct marrow suppression and hepatosplenic sequestration. Platelet thromboxane B₂ production is also temperature-dependent (Valeri et al. 1987). Paradoxically, rewarming the hypothermic patient reverses the hypothermia-induced thrombocytopenia and decreases clotting time.

Rewarming Techniques

Although it is thought that duration of exposure is a prime factor in determining which kind of rewarming will reverse hypothermia most effectively, no data exists to support this contention. The pivotal treatment decision is between passive and active rewarming. Choice of method is based on the degree of expertise and experience of a particular group and available facilities, rather than on the degree of hypothermia (Golden 1983) (Figure 4).

Since chronic hypothermia induces fluid sequestration, direct application of heat to the extremities can extinguish peripheral vasoconstriction (that can overwhelm a depressed cardiovascular system with volumetric, metabolic, and electrolyte flux demands). Thus, limiting heat application to the trunks of acutely hypothermic patients minimizes the systemic physiologic concerns that often accompany active, total-body external rewarming.

Another concern is core temperature afterdrop (the continued fall in core temperature after rewarming is instituted), which might further decrease the myocardial temperature and lead to ventricular fibrillation (Olsen 1988). The explanation of afterdrop is still under debate with evidence suggesting it is a purely physical or physiological phenomenon (Golden 1983; Hayward, Eckeson, and Kemna 1984). Afterdrop does not always occur during rewarming, since it depends on such factors as degree of hypothermia and the method of rewarming.

Passive external rewarming is appropriate in mild cases of hypothermia. Covering and insulating the skin minimizes further heat loss in a patient who must maintain a steady rate of rewarming by utilizing their metabolism (Shields and Sixsmith 1990; Erickson and Yount 1991). Sufficient endogenous thermogenesis is usually impossible below 32°C because of hypothermia-induced poikilothermia.

Active rewarming involves direct transfer of exogenous heat to the patient, either externally or internally. Options for active external rewarming (AER) include forced air, electric or plumbed heating blankets, radiant heat sources, and immersion (Romet and Hoskin 1988; Hauty, et al. 1987). Although conditions mandating active rewarming are noted in Figure 4, mild hypothermia may also be

treated using active rewarming techniques. Clinical concerns accompanying these rewarming technologies range from thermal injury (burns) of hypoperfused vasoconstricted skin, to the difficulty of monitoring and administering therapy to a patient immersed in warm water (Danzl, Pozos, and Hamlet 1989; Miller, Danzl, and Thomas 1980).

Detrimental tissue oxygenation factors abound, especially with the demands of rewarming. The shift to the left of the oxyhemoglobin dissociation curve impedes oxygen release. Tissue hypoperfusion through vasoconstricted plexi offers additional impedance. The "functional" value of hemoglobin at 28°C is only 40% of what it would be at 37°C (Danzl, Pozos, and Hamlet 1989). Caloric heat transfer during infusion of intravenous fluids during peak flow at 40°C to 42°C is marginal. One liter of fluid at 42°C infused into a 70 kg patient (60% total body weight) at 28°C will raise the core temperature only one third of one degree. In volume-depleted or exsanguinated patients, single, counter-current heat exchanges will efficiently heat and deliver crystalloids and colloids.

Active core rewarming (ACR) techniques deliver heat internally. Options include airway rewarming, heated infusions and irrigation, diathermy, and extracorporeal rewarming (ECR). Airway rewarming with heated, humidified oxygen < 45°C is a valuable adjunct. It should be emphasized that this latter method does not increase body temperature and, at best, will minimize body heat loss from the respiratory system. Only complete humidification maximizes the limited amount of transferable heat. Humidified airway rewarming helps decrease pulmonary secretion viscosity and cold-induced bronchorrhea, while stimulating pulmonary cilia. Hypothermic ventilation-perfusion mismatch, depressed respiratory minute volume, and atelectatic changes are attenuated without adverse effects on surfactant (Lloyd 1991). Heated inhalation is a commonly selected rewarming adjunct coupled with PER in mild cases, and with other, more invasive techniques in severe cases (Miller, Danzl, and Thomas 1980; Otto and Metzler 1988).

Peritoneal dialysate at 40 to 45°C conducts heat efficiently to the intraperitoneal structures (Moss et al. 1986). The common procedure is to infuse at least 20 cc/kg up to 2L, allow it to thermally equilibrate for 20 minutes, and aspirate. Double-catheter systems with outflow suction yield exchange rates approaching 6L/hr. The patient's size and physiological status impact the rewarming rate, which ranges from 2 to 3°C/hr. Unique considerations include direct rewarming of hepatic detoxification enzymes, and manipulation of serum potassium fluctuations. Generally, this invasive technique is reserved for rewarming severely hypothermic patients and for combination rewarming of nonperfusing patients (Otto and Metzler 1988). Caloric transfer resulting from irrigation of either end of the gastrointestinal tract or the urinary bladder is ineffective. Limitations are imposed by available surface area, absorption-induced fluid, and electrolyte fluxes.

Thoracic cavity lavage is an attractive alternative warranting investigation for nonperfusing patients (Otto and Metzler 1988; Hall and Syverud 1990). Continuous bilateral afferent and efferent thoracostomy tube irrigation will transfer heat rapidly (Iversen et al. 1990). Mediastinal and direct cardiac lavage should be considered only when ECR is indicated, but is not a viable option.

The technique of extracorporeal rewarming via cardiopulmonary bypass guarantees perfusion coupled with a steep rewarming curve (Althaus et al. 1982; Walpoth et al. 1990), and should be considered for cardiac arrest patients, or for those with multiple system trauma, frozen extremities, rhabdomyolysis, or profound hypothermia (Hauty et al. 1987). The availability of heparin-bonded circuits expands horizons and simplifies coagulative titration (Del Rossi, Cernaianu, and Vertrees 1990). Bypass flow rates should be initiated at 2 to 3 L/min, and gradually increased up to 6L/min (Long 1992). Thawing is brisk, ranging from 4 to more than 9.5°C/hr (Splittgerber et al. 1986). Endothelial leakage may necessitate massive volume supplementation, and extreme hyperkalemia will mandate hemodialysis.

Percutaneous cannulation of vessels with two-way flow catheters is another rewarming technique (Gregory et al. 1991; Gentilello and Rifley 1991). Accelerated rewarming potentially exacerbates hemolysis, disseminated intravascular coagulation, acute tubular necrosis, and adult respiratory distress syndrome. ECR should be discontinued if intravascular thrombosis is identified or CPR contraindications appear.

Rewarming Issues

Most hypothermic patients have depressed thirst, increased vascular permeability, fluid sequestration, and elevated blood viscosity ($2\%/1^{\circ}\text{C}$ hypothermia). Adequate crystalloid/colloid resuscitation is particularly critical in chronic or secondary hypothermia (Bangs 1984). Therefore, it is safe to assume initially that most patients will benefit from rapid volume expansion during rewarming; however, due to the system's fragility, as well as the potential of other complications, it is important to monitor for evidence of fluid overload.

Pharmacologic activity in hypothermic patients differs from normothermia and is largely temperature-dependent. Protein-binding increases, enterohepatic circulation and renal excretion are altered, and target organs become physiologically less responsive. During profound hypothermia, rewarming can transform substandard therapeutic activity (e.g., insulin or digoxin) to toxicity (Wang 1983). Since the vasculature should be maximally constricted to minimize heat loss, pharmacological manipulations are usually avoided. Low-dose catecholamine infusions potentially jeopardize frostbitten tissues, and should be reserved for refractory hypotensions disproportionate to the temperature (Chernow et al. 1983).

A variety of atrial arrhythmias that present with a slow ventricular response are common (Danzl et al. 1987). Unless pre-existent, these rhythms should be considered innocuous and left untreated, since they inevitably convert spontaneously during rewarming. The issues surrounding ventricular

antiarrhythmic selection, dosage, rate of infusion, toxicity, and prophylaxis are unresolved. Bretylium tosylate has documented antiarrhythmic activity during hypothermic conditions in several animal studies, with two clinical cases of spontaneous chemical defibrillation reported (Murphy, Nowak, and Tomlanovich 1986). Lidocaine appears far less effective. Bradyarrhythmias will refract atropine. Transvenous intracardiac pacing of a perfusing rhythm is extremely hazardous; transthoracic pacing would seem preferable, but only as a last resort.

Acute cold stress stimulates cortisol and adrenal corticotrophic hormone (ACTH) secretion. Functional adrenal insufficiency is difficult to establish, since false diagnosis can occur due to cold-induced adrenal unresponsiveness to ACTH (Felicetta, Green, and Goodner 1980). Considerations preceding empiric replacement should include a history of steroid dependence, suspicion of hypoadrenocorticism, or an inexplicable failure to rewarm.

Carefully consider hypothermic myxedema in chronically hypothyroid patients with an infectious, metabolic, traumatic, or toxicologic stress. Suggestive physical stigmata should be sought; they occur most frequently in the elderly and in females. Hypothermia usually increases both the contraction and relaxation times of the Achilles tendon reflex, but interestingly, the relaxation phase is particularly prolonged in hypothermic myxedema (MacLean, Taig, and Emslie-Smith 1973). Previously undiagnosed patients, or those whose rate of rewarming is slower than predicted, present a therapeutic challenge. Avoid empiric therapy with parenteral l-thyroxin, but remain aware that delayed recognition and therapy often increases the risk to a euthyroid hypothermic patient (Danzl, Pozos, and Hamlet 1989).

Post-Rewarming Considerations

Cardinal historical, physical, vital sign, and laboratory cues suggesting an antecedent or coexistent infection are variably misleading. Inflammatory responses are minimized. In the absence of fever and tachycardia, rigors mimic shivering. Similarly, impaired marrow release, neutrophil circulation and

migration, and bacterial phagocytosis produce leukopenia. Because of the resultant infectious complications, some clinicians have abandoned therapeutic maintenance of cerebra-protective hypothermia in near-drowning victims (Bohn et al. 1986). The indications for, and the extent of, pan-culturing must be liberalized from normothermia. A clinical picture consistent with secondary hypothermia, or failure to rewarm, should arouse suspicion. Antimicrobial prophylaxis is often warranted in neonates and the elderly (Kramer, Vandijk, and Rosin 1989; Gautam et al. 1989).

Disposition is predicated on the etiology and severity of hypothermia. Patients rewarmed from mild primary hypothermia are dischargeable to a warm environment. Those with a more severe temperature depression, or with secondary hypothermia (Table 2), usually require prolonged evaluation and monitoring (Danzl, Pozos, and Hamlet 1989).

Outcome

Successful resuscitation of patients with accidental hypothermia requires careful consideration of any pre-existent or cold-induced pathophysiology. Hypothermia is both masked by and masquerades as a variety of processes. The challenge lies in both its recognition and in the implementation of a versatile approach to therapy. Resuscitative permutations entail simultaneous and sequential use of numerous rewarming modalities. Assessing the potential for recovery would be dually valuable. Clearly, "some people are dead when they're cold dead," and implementation of cardiopulmonary bypass would be inappropriate (Auerbach 1990). Furthermore, selection bias affects interpretation of the therapeutic response attributed to specific rewarming modalities. Therefore, the concept of a validated Hypothermia Outcome Score is attractive (Danzl et al. 1987). Reported grave prognostic indicators, such as trauma, infection, toxin ingestion, or hyperkalemia (> 10 mg/L) variably impact survival (Hauty et al. 1987; Jurkovich et al. 1987; Schaller, Fischer, and Perret 1990). Unlike the discovery of intravascular thrombosis, their isolated presence does not justify

aborting initial resuscitative efforts. Hence, the old dictum, "No one is dead until they are warm and dead," should be considered until the patient has been rewarmed to 30 to 32°C (Southwick and Dalglish 1980).

Hypothermia in the Surgical Patient - Perioperative Hypothermia

Although this review focuses on the accidental hypothermia victim, most of the treatment and rewarming issues also apply to iatrogenic hypothermia. The major difference lies in the fact that in iatrogenic hypothermia, the clinician is aware of the cause, duration, and magnitude of the hypothermic condition.

There has been increased awareness among anesthesia and surgical personnel of hypothermia's consequences, such that steps are being taken to minimize hypothermia in the operating room. General anesthesia causes mild hypothermia by interfering with hypothalamic control (Imrie and Hall 1990), whereas regional anesthesia may provoke hypothermia by increased vasodilation in the operating room's cool environment (Sessler and Ponte 1989).

In perioperative situations, cold-induced metabolic increase adds an additional burden to the patient both physiologically and psychologically. In one study, an analysis of the subjective reactions of patients arriving in the recovery room revealed that approximately 60% had a clear recollection of "freezing to death" (Jurkovich et al. 1987). However, these heat-producing mechanisms could be counterproductive in a clinical setting. Myocardial oxygen consumption is increased, and postoperative hypertension may develop with consequent myocardial ischemia in patients with myocardial disease. Active rewarming techniques and various shiver-suppressing medications are commonly used. Although a majority of these patients demonstrate similar thermal responses (as if in primary hypothermia), isolated cases of postoperative shaking not representing shivering indicate that additional studies in these areas are warranted (Schaller, Fischer, and Perret 1990; Southwick and Dalglish 1980).

Future Clinical Challenges of Hypothermia

Although hypothermia has been identified and treated since ancient times, its advantages and liabilities continue to challenge the clinician. Recently, treating mild hypothermia using cold liquid to cool the head has been reported to minimize the consequence of cerebral anoxia in dogs in whom ventricular fibrillation was induced and EEG activity had ceased for ten minutes (Leonov et al. 1990). The reported use of convective cooling to induce mild hypothermia in anesthetized dogs could be a useful tool in select neurosurgical and vascular surgery patients (Southwick and Dalglish 1980).

Conversely, although beneficial effects attend mild and moderate hypothermia, a drop in core temperature severely stresses physiologic systems and will represent a continuing challenge to physicians, whether in the Emergency Room or the Postanesthetic Care Unit.

Figure Legends

- Figure 1: Model of thermoregulatory system, its reaction to cold stress, and resultant increase in core temperature. Shaded area demonstrates role of multiple central nervous system structures integrating various cold thermal receptor inputs.
- Figure 2: Model of effects of hypothermia on thermoregulatory system and resultant decrease in core temperature.
- Figure 3: Model of various sites in thermoregulatory system which can be compromised to induce secondary hypothermia and resultant drop in core temperature.
- Figure 4: Flow diagram of recommended procedures for treatment of hypothermia.
- Table 1: Clinical signs of decreasing core temperature demonstrating hypothermia-induced depression of physiological systems.
- Table 2: Various conditions that will predispose toward hypothermia.

References

- Althaus, U., P. Aeberhand, and P. Schupbach, et al. 1982. Management of profound accidental hypothermia with cardiorespiratory arrest. *Annals of Surgery* 195:492-95.
- Auerbach, P.S. 1990. Some people are dead when they're cold and dead. [Editorial] *JAMA* 264:1856-57.
- Bangs, C.C. 1984. Hypothermia and Frostbite. *Emergency Medicine Clinics of North America* 2:475-87.
- Bligh, J. 1985. Regulation of body temperature in man and other mammals. In: Heat Transfer in Medicine and Biology Analysis Application. Vol 1 Pages 15-51. Edited by A. Shitzer and R.C. Eberhart. Plenum Press.
- Bohn, D.J, W.D. Biggar, C.R. Smith, et al. 1986. Influence of hypothermia, barbiturate therapy and intracranial pressure monitoring on morbidity and mortality after near drowning. *Critical Care Medicine* 14:529-34.
- Chernow, B., C.R. Lake, A. Zaritsky, et al. 1983. Sympathetic nervous system "switch off" with severe hypothermia. *Critical Care Medicine* 11:677-80.
- Danzl, D.F, R.S. Pozos, and M.P. Hamlet. 1989. Accidental Hypothermia. In: Management of Wilderness and Environmental Emergencies, Mosby, 1989, Auerbach and Geehr; second edition (p35-76).
- Danzl, D.F, R.S. Pozos, P.S. Auerbach, et al. 1987. Multicenter hypothermia survey. *Annals of Emergency Medicine* 16:1042-55.

- Del Rossi, A.J., A.C. Cernaianu, and R.A. Vertrees. 1990. Heparinless extracorporeal bypass for treatment of hypothermia. *Journal of Trauma* 30:79-82.
- Delaney, K.A., M.A. Howland, S. Vassallo, et al. 1989. Assessment of acid-base disturbances in hypothermia and their physiologic consequences. *Annals of Emergency Medicine* 18:72-82.
- Erickson, R.S., and S.T. Yount. 1991. Effect of aluminized covers on body temperature in patients having abdominal surgery. *Heart Lung* 20:255-64.
- Felicetta, J.V., W.L. Green, and C.J. Goodner. 1980. Decreased adrenal responsiveness in hypothermic patients. *Journal of Clinical Endocrinology and Metabolism* 50:93-97.
- Feroe, D.D., and S. Augustine. 1991. Hypothermia in PACU Critical Care Nursing. *Clinics of North America* 3:135-144.
- Ferrara, A., J.D. MacArthur, H.K. Wright, et al. 1990. Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *American Journal of Surgery* 160:515-18.
- Gautam, P., S. Ghosh, A. Mandel, et al. 1989. Hypothermia in the elderly: sociomedical characteristics and outcome of 86 patients. *Public Health* 103:15-22.
- Gentilello, L.M., and W.J. Rife. 1991. Continuous arteriovenous rewarming: report of a new technique for treating hypothermia. *Journal of Trauma* 31:1151-54.

- Golden F St. C. 1983. Rewarming In: The Nature and Treatment of Hypothermia. Chapter 16 pp. 194-208. Editors RS Pozos, LE Wittmers, University of Minnesota, Minneapolis.
- Gregory, J.S., J.M. Bergstein, C. Aprahamian, et al. 1991. Comparison of three methods of rewarming from hypothermia: advantages of extracorporeal blood rewarming. *Journal of Trauma* 31:1247-52.
- Hall, K.N., and S.A. Syverud. 1990. Closed thoracic cavity lavage in the treatment of severe hypothermia in human beings. *Annals of Emergency Medicine* 19:204-06.
- Hamlet, M.P. 1987. An overview of medically related problems in the cold environment. *Military Medicine* 152:393-96.
- Hauty, M., B. Esrig, J. Hill, and W.B. Long. 1987. Prognostic factors in severe accidental hypothermia: experience from the MT Hood tragedy. *Journal of Trauma* 27:1107-12.
- Hayward, J.S., J.D. Eckeson, and D. Kemna. 1984. Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation* 11:21-33.
- Imrie, M.M., and G.M. Hall. 1990. Body temperature and anesthesia. *British Journal of Anaesthesia* 64:346-54.
- Iversen, R.J., S.H. Atkin, M.A. Jaker, et al. 1990. Successful CPR in severe hypothermic patient using continuous thoracostomy lavage. *Annals of Emergency Medicine* 19:1335-37.

- Jurkovich, G.J., W.B. Greiser, A. Luterman, et al. 1987. Hypothermia in trauma victims: an ominous predictor of survival. *Journal of Trauma* 27:1019-24.
- Kaufman, W.C. 1982. Physiological evaluation of levels of hypothermia and effectiveness of recovery technique. In: *Human Performance in the Cold*. (eds) G Larsen, RS Pozos, F Hempel. Publisher: Undersea Medicine Soc. Inc.
- Kramer, M.R., J. Vandijk, and A.J. Rosin. 1989. Mortality in elderly patients with thermoregulatory failure. *Archives of Internal Medicine* 149:1521-23.
- Kroncke, G.M., R.D. Nichols, and J.T. Mendenhall. 1986. Ectothermic philosophy of acid-base balance to prevent fibrillation during hypothermia. *Archives of Surgery* 121:303-04.
- Leonov, Y., F. Sterz, R. Safar, et al. 1990. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. *Journal of Cerebral Blood Flow & Metabolism* 10:57-70.
- Lloyd, E.L. 1991. Equipment for airway warming in the treatment of accidental hypothermia. *Journal of Wilderness Medicine* 2:33-50.
- Long, W.B. 1992. Cardiopulmonary bypass for rewarming profound hypothermia patients. Annual International Forum; Critical Decisions in Hypothermia, Portland, Oregon.
- MacLean, D., D.R. Taig, and D. Emslie-Smith. 1973. Achilles tendon reflex in accidental hypothermia and hypothermic myxedema. *British Journal of Medicine* 2:87-90.

- Miller, J.W., D.F. Danzl, and D.M. Thomas. 1981. Hypothermia Treatment. *Annals of Emergency Medicine* 10:396-400.
- Miller, J.W., D.F. Danzl, and D.M. Thomas. 1980. Urban accidental hypothermia: 135 cases. *Annals of Emergency Medicine* 9:456-61.
- Mills, W.J. Jr. 1980. Accidental hypothermia: management approach. *Alaska Medicine* 22:9-11.
- Moss, J.F., M. Haklin, H.W. Southwick, and D.L. Roseman. 1986. A model for the treatment of accidental severe hypothermia. *Journal of Trauma* 26:68-74.
- Murphy, K., R.M. Nowak, and M.C. Tomlanovich. 1986. Use of bretylium tosylate as prophylaxis and treatment in hypothermic ventricular fibrillation in the canine model. *Annals of Emergency Medicine* 15:1160-66.
- Nicholson, R.W., and K.V. Iserson. 1991. Core temperature measurement in hypovolemic resuscitation. *Annals of Emergency Medicine* 20:262-65.
- Olsen, R.G. 1988. Reduced temperature afterdrop in rhesus monkeys with radio frequency rewarming. *Aviation Space and Environmental Medicine* 59:78-80.
- Otto, R.J., and M.H. Metzler. 1988. Rewarming from experimental hypothermia: comparison of heated aerosol inhalation, peritoneal lavage and pleural lavage. *Critical Care Medicine* 16:869-75.
- Paton, B.C. 1983. Accidental hypothermia. *Pharmacology and Therapeutics* 22:331-77.

- Patt, A., B.L. McCroskey, and E.E. Moore. 1988. Hypothermia-induced coagulopathies in trauma. *Surgical Clinics of North America* 68:77-85.
- Poulos, N.D., and D.L. Mollitt. 1991. The nature and reversibility of hypothermia-induced alterations of blood viscosity. *Journal of Trauma* 31:996-1000.
- Pozos, R.S., and P.A. Iaizzo. 1991. Shivering and pathological and physiological clonic oscillations of the human ankle. *Journal of Applied Physiology* 71(5):1929-32.
- Reed, R.L., A.W. Bracey, J.D. Hudson, et al. 1990. Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels. *Circulatory Shock* 32:141-52.
- Romet, T.T., and R.W. Hoskin. 1988. Temperature and metabolic responses to inhalation and bath rewarming protocols. *Aviation Space and Environmental Medicine* 59:630-34.
- Schaller, M.D., A.P. Fischer, and C.H. Perret. 1990. Hyperkalemia. A prognostic factor during acute severe hypothermia. *JAMA* 264:1842-45.
- Sessler, D.F., and J. Ponte. 1989. Hypothermia during epidural anesthesia results mostly from redistribution of heat within the body not heat loss to the environment. *Anesthesiology* 71:A882.
- Shields, C.P., and D.M. Sixsmith. 1990. Treatment of moderate-to-severe hypothermia in an urban setting. *Annals of Emergency Medicine* 19:1093-97.

- Shiraki, K., S. Sagawa, F. Tajima, et al. 1988. Independence of brain and tympanic temperature in an unanesthetized human. *Journal of Applied Physiology* 65(1):482-486.
- Simon, E. 1966. Kaltezhein bei Narkotisierten Spinalen Huuden. *Pflugers Archives* 291:187-204.
- Solomon, A., R.A. Barish, B. Brown, et al. 1989. The electrocardiographic features of hypothermia. *Journal of Emergency Medicine* 7:169-73.
- Southwick, F.S., and P.H. Dalglish. 1980. Recovery after prolonged asystole cardiac arrest in profound hypothermia. *JAMA* 243:1250-53.
- Splittgerber, F.H., J.G. Talbert, W.P. Sweezer, et al. 1986. Partial cardiopulmonary bypass for core rewarming in profound accidental hypothermia. *Annals of Surgery* 52:407-12.
- Steinman, A.M. 1986. Cardiopulmonary resuscitation and hypothermia. *Circulation* 74:29-32.
- Swain, J.A. 1988. Hypothermia and blood pH: a review. *Archives of Internal Medicine* 148:1643-46.
- Valeri, C.R., H. Feingold, G. Cassidy, et al. 1987. Hypothermia-induced reversible platelet dysfunction. *Annals of Surgery* 205:175-81.
- Voelsang, J., and S. Hayes. 1989. STADOL attenuates postanesthesia shivering. *Journal of Post Anesthesia Nursing* 4:222-27.

- Walpoth, B.H., R. Locher, F. Leupi, et al. 1990. Accidental deep hypothermia with cardiopulmonary arrest: extracorporeal blood rewarming in 11 patients. *European Journal of Cardio-Thoracic Surgery* 4:390-93.
- Wang, K.C. 1983. Physiology and pharmacology of hypothermia. *Western Journal of Medicine* 138:227-32.
- White, F.N. 1983. Reassessing acid-base balance in hypothermia: a comparative point of view. *Western Journal of Medicine* 138:255-57.

Acknowledgements

We are indebted to Sue Sobanski for editorial review and manuscript preparation. Mr. Don Hogue prepared the illustrations and was partially supported by a grant from Augustine Medical Inc. Critical review of this document was rendered by A. Pozos, M.D., University of California, San Diego.

Fig. 1. COLD STRESS

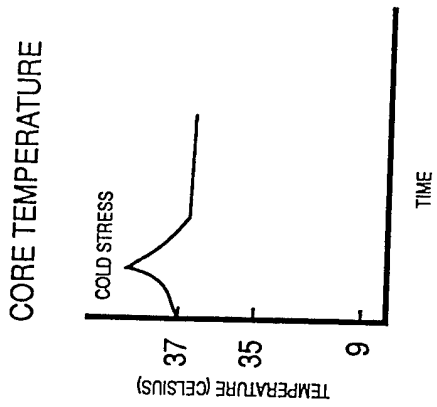
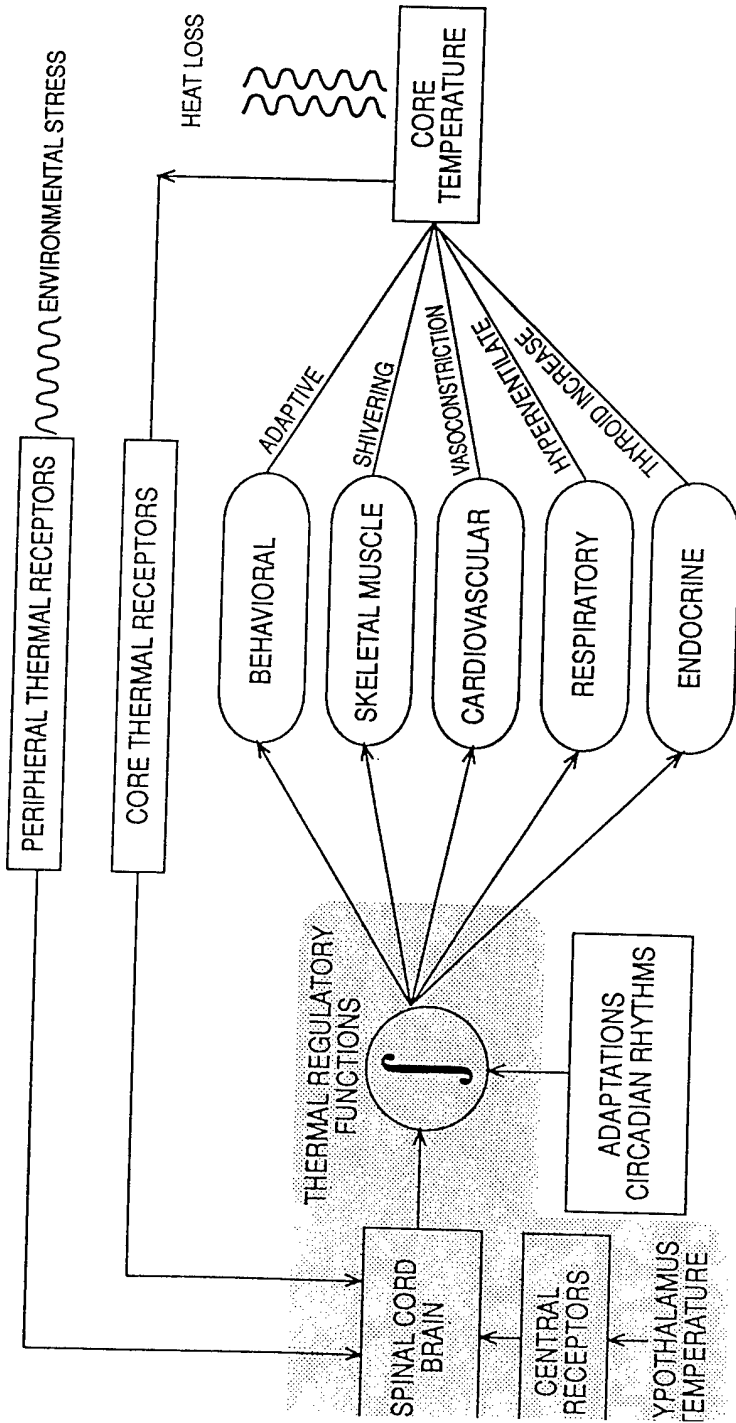


Fig. 2. PRIMARY HYPOTHERMIA

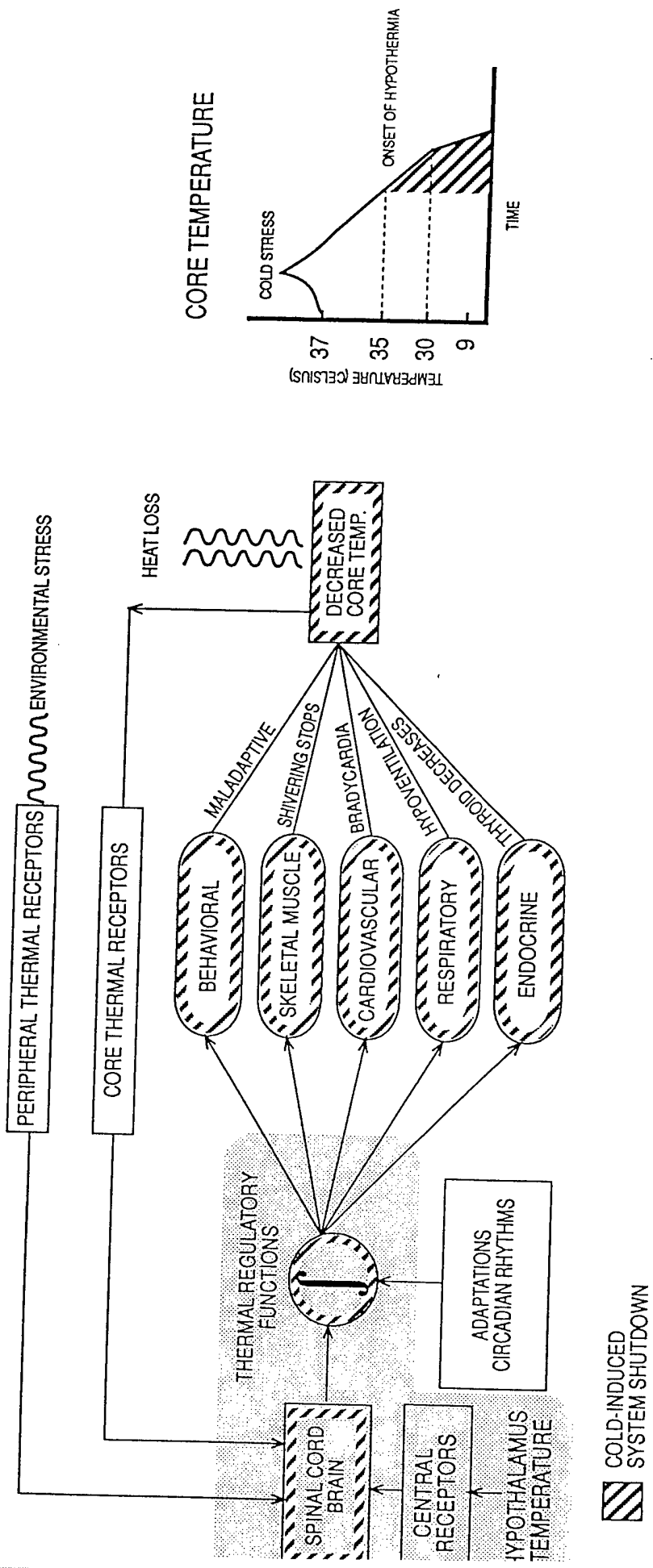


Fig. 3. SECONDARY HYPOTHERMIA

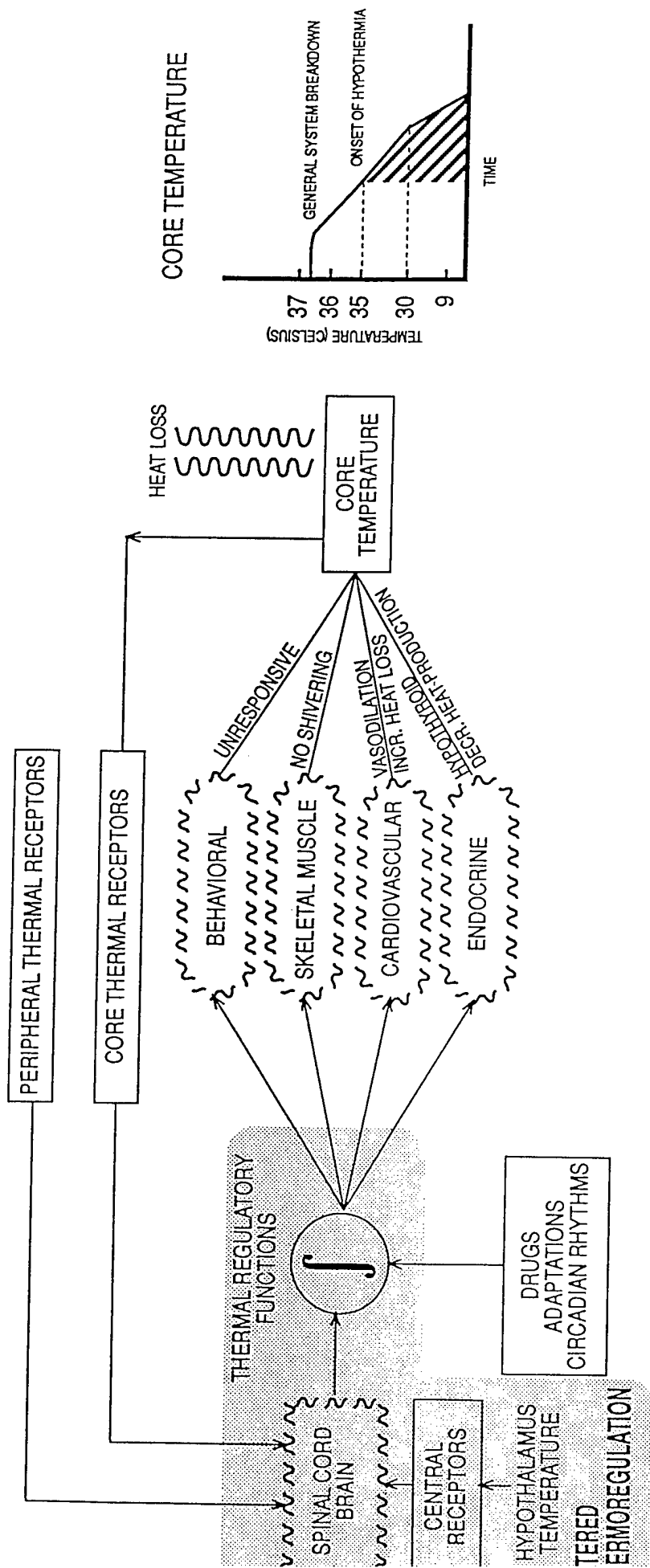
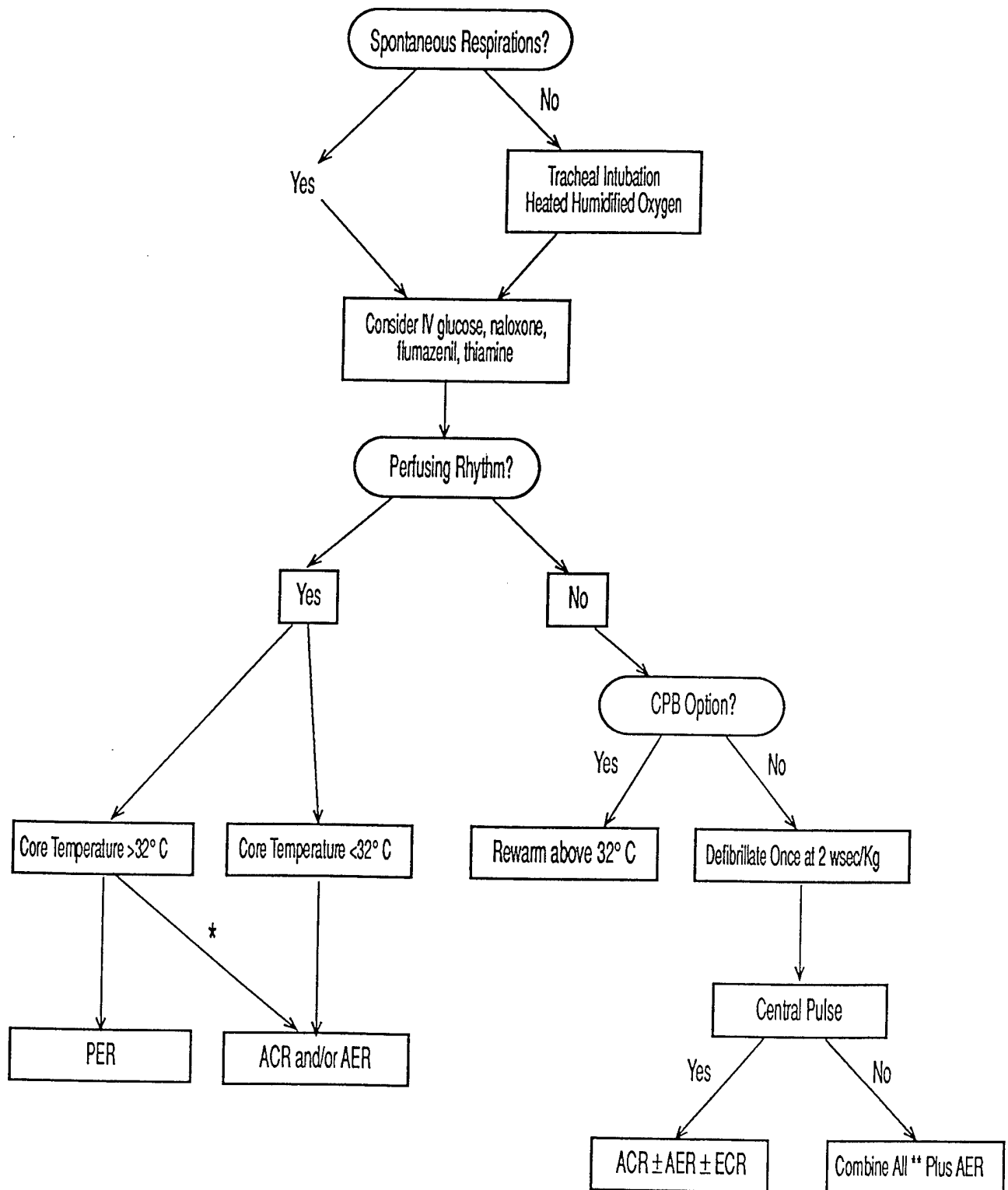


Fig. 4. Advanced Hypothermic Life Support



Legend

PER = passive external rewarming
AER = active external rewarming
ACR = active core rewarming

CPB = cardiopulmonary bypass
ECR = extracorporeal rewarming

* If C-V instability; poikilothermia; T-R dysfunction; endocrinologic insufficiency; age extremes; traumatic/toxicologic vasodilation.

** Airway rewarming; heated irrigation (peritoneal, thoracic, GI); IV's; ECR; CPB; diathermy (investigational).

TABLE 1: HYPOTHERMIA INDUCED PHYSIOLOGICAL CASCADE

	CNS	Cardiovascular	Respiratory	Renal	Neuromuscular
35°C ↓ 31°C	Linear depression of cerebral metabolism: amnesia, apathy, dysarthria, impaired judgment; maladaptive behavior	Tachycardia, then progressive bradycardia. Cardiac cycle prolongation; Hematocrit ↑ 2%/1°C	Tachypnea, then progressive ↓ RMV; declining O ₂ consumption	'Cold diuresis' of 'GF'	Increased pre-shivering muscle tone; then fatiguing shivering thermogenesis
30°C	EEG abnormalities; progressive depression of VEP's and LOC; poikilothermia; pupillary dilation	Progressively severe depression of pulse and C.O.; increasing atrial and ventricular arrhythmias; nonspecific and suggestive (J wave) EKG changes	Hypoventilation; 50% ↓ CO ₂ production/8°C; Protective airway reflexes absent	RBF ↓ 50%	Hyporeflexia: extinguishing shivering thermogenesis
25°C	Loss of cerebro-vascular autoregulation; CBF declines	50% bradycardia; 45% cardiac output; re-entrant dysrhythmias; ↓ VF threshold	Pulmonic congestion	Glomerular hypofiltration; poor nitrogenous clearance	Motionless; 'peripheral' areflexia
20°C	EEG Silencing	20% bradycardia; severe ↓ VF threshold; asystole	75% ↓ O ₂ consumption	Extreme oliguria	'brainstem' areflexia
16°C	Lowest adult accidental hypothermia survivor				
15.2°C	Lowest infant accidental hypothermia survivor				
9°C	Lowest therapeutic hypothermia survivor				

TABLE 2

FACTORS PREDISPOSING TO HYPOTHERMIA

Decreased heat production

Endocrinologic failure
 Hypopituitarism
 Hypoadrenalism
 Hypothyroidism
 Lactic acidosis, DKA, AKA
 Insufficient fuel
 Hypoglycemia
 Malnutrition
 Marasmus
 Kwashiorkor
 Physical exertion, e.g., marathon
 Neuromuscular inefficiency
 Age extremes
 Impaired shivering
 Inactivity

Impaired thermoregulation

Peripheral failure
 Neuropathies
 Acute spinal cord transection
 Diabetes
 Central failure/Neurologic
 CNS trauma
 CVA
 Toxicologic
 Metabolic
 Subarachnoid hemorrhage
 Pharmacologic
 Hypothermic dysfunction
 Parkinson's disease
 Anorexia nervosa
 Cerebellar lesion
 Neoplasm
 Congenital intracranial anomalies
 Multiple sclerosis
 Hypereplemic periodic paralysis

Increased heat loss

Environmental
 Immersion
 Nonimmersion
 Induces vasodilation
 Pharmacologic
 Toxicologic
 Erythrodermas
 Burns
 Psoriasis
 Ichthyosis
 Exfoliative dermatitis
 Iatrogenic
 Emergent deliveries
 Cold infusion
 Heat stroke treatment

Misc associated clinical states

Multisystem trauma
 Recurrent hypothermia
 Episodic hypothermia (Shapiro's syndrome)
 Infectious-bacterial, viral parasitic
 Pancreatitis
 Carcinomatosis
 Cardiopulmonary disease
 Vascular insufficiency
 Uremia
 Paget's disease
 Giant cell arteritis
 Sarcoidosis
 Shaken baby syndrome
 Systemic lupus
 Wernicke-Korsakoff
 Hodgkin's disease
 Shock
 Sick cell anemia

REPORT DOCUMENTATION PAGE

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503

1. AGENCY USE ONLY (Leave blank)**2. REPORT DATE**

7-16-93

3. REPORT TYPE & DATE OVERED

Chapter

4. TITLE AND SUBTITLE

Hypothermia

5. FUNDING NUMBERS

Program Element:

Work Unit Number:

ONT Reimbursable

6. AUTHOR(S)

R.S. Pozos, P.A. Iazzo, D.F. Danzl

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Naval Health Research Center

P.O. Box 85122

San Diego, CA 92186-5122

8. PERFORMING ORGANIZATION

Report No. 93-8

9. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)

Naval Medical Research and Development Command

National Naval Medical Center

Building 1, Tower 2

Bethesda, MD 20889-5044

**10. SPONSORING/MONITORING
AGENCY REPORT NUMBER****11. SUPPLEMENTARY NOTES****12a. DISTRIBUTION/AVAILABILITY STATEMENT**

Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

A

13. ABSTRACT (Maximum 200 words)

Man has a complex, physiologically coordinated system designed to maintain a core temperature of 37°C. Despite the amazing capacity and responsiveness of the thermoregulatory system, human health is frequently challenged by cold stress leading to hypothermia. Recently, unpredictable climatic conditions were responsible for the deaths of five mountaineers on Mount McKinley. The incidence of hypothermia is not limited to cold latitudes. Hypothermia may occur in even tropical regions. Add to this the many cases of cold water exposure and hypothermia secondary to trauma, and it is clear that accidental hypothermia due to environmental cold conditions is a very real concern for clinicians.

External factors, however, are not the only causes of hypothermia. Indeed, hypothermia is frequently the result of anesthesia or drugs that interfere with internal thermoregulatory mechanisms. Annually, between one and seven million patients in postanesthetic care units experience mild hypothermia. The expense and threat to human health, especially in patients with compromised conditions associated with cardiovascular, endocrine, and degenerative disorders, is just beginning to be recognized and evaluated. This review will focus on the current understanding of human thermoregulation, the common basis for understanding various categories of hypothermia, and therapeutic approaches to its management and treatment.

14. SUBJECT TERMS

Hypothermia

Drugs

15. NUMBER OF PAGES

33

16. PRICE CODE**17. SECURITY CLASSIFI-
CATION OF REPORT**

Unclassified

**18. SECURITY CLASSIFI-
CATION OF THIS PAGE**

Unclassified

**19. SECURITY CLASSIFI-
CATION
OF ABSTRACT**

Unclassified

20. LIMITATION OF ABSTRACT

Unclassified